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# Severe thrombophilia with antiphospholipid syndrome and hyperhomocysteinemia in a patient with Schnitzler's syndrome

G. Famularo, A. Barracchini[1], G. Minisola[1]

*Department of Internal Medicine III and [1]Department of Rheumatology, San Camillo Hospital, Rome, Italy.*

*Please address correspondence to: Dr. Giuseppe Famularo, Department of Internal Medicine, Ospedale San Camillo, Circonvallazione Gianicolense, 00152 Rome, Italy. E-mail: gfamularo@uni.net*

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**ABSTRACT**

*Schnitzler's syndrome is a rare condition with chronic urticaria, intermittent fever, bone pain, and a monoclonal IgM gammopathy. Most patients have a chronic and indolent course, but a small number ultimately progress to a lymphoplasmacytic malignancy. We describe a patient with Schnitzler's syndrome who entered an accelerated phase of clinical deterioration with repeated thromboses of the cerebral and coronary arteries that ultimately led to a fatal outcome. We found that the he fulfilled the Sapporo criteria for definite antiphospholipid syndrome and had elevated blood levels of homocysteine during the active clotting phase of the disease. We suggest that the association with immune-mediated or metabolic disorders, such as the antiphospholipid syndrome and hyperhomocysteinemia, may unfavorably affect the otherwise chronic and stable course of patients with Schnitzler's syndrome. The systemic clotting disorder, the association with the antiphospholipid syndrome and hyperhomocysteinemia, and the biclonal rather than monoclonal IgM gammopathy were striking features of this atypical case of Schnitzler's syndrome.*

## Introduction

Schnitzler's syndrome is a rare condition with a unique and particular constellation of chronic urticaria, intermittent fever, bone pain, arthralgia or arthritis, and a monoclonal IgM gammopathy in a concentration that is usually less than 100 mg/dL (1). The syndrome was first described by Schnitzler, a French dermatologist, in 1974 (2) and since then no more than fifty other patients have been reported. Thrombosis and an association with the antiphospholid syndrome or hyperhomocysteinemia have not been observed so far in patients with this disorder.

We describe a patient with Schnitzler's syndrome complicated by the antiphospholipid syndrome and hyperhomocysteinemia who had recurrent cerebral and coronary thromboses with a fatal outcome.

## Case report

A 64-year-old man presented in 1993 with a 2-year course of recurrent self-limiting fever (with temperature peaks as high as 40°C), chronic non-pruritic urticaria, and bone pain. Episodes of fever and urticaria usually resolved within 24-48 hours. With the exception of widespread uritcarial lesions, the physical examination was otherwise normal.

Laboratory investigations showed an increased erythrocyte sedimentation rate (ESR) of 75 mm/h with a C reactive protein level of 17.8 mg/dL. Serum protein electrophoresis demonstrated two monoclonal IgM components with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. Total IgM was 1580 mg/dL (normal, 60–260 mg/dL) and IgG 553 mg/dL (normal, 694-1618 mg/dL); IgA, IgD, and C1 inhibitor were within the normal range. C3 was 78 mg/dL (normal, 88-201 mg/dL) and C4 < 10 mg/dL (normal, 16-47 mg/dL) There were no antinuclear antibodies, antineutrophil antibodies, cold agglutinins, cryofibrinogen, or cryoglobulins. Antibodies to myelin glycoprotein were absent. An IgM anti-IgG rheumatoid factor was present at 390 U/ml (normal < 20 U/mL). Hepatitis B and C was excluded. Creatinine, complete blood count, coagulation studies, and serum calcium were in the normal range.

Skeletal X-rays were normal with the exception of hyperostosis of the ninth right-sided rib. A computed tomographic scan of the brain, chest and abdomen was also normal and a bone marrow biopsy showed no abnormality.

A biopsy of an urticarial lesion showed edema and a perivascular infiltrate of neutrophils and eosinophils in the papillary dermis,that were considered consistent with neutrophilic urticaria. Immunofluorescence studies did not reveal immune globulin or complement deposition.

Treatment with antihistamines (loratadine, terfenadine, dexchlorpheniramine, hydroxyzine), colchicine (1mg/d), dapsone (100 mg/d), aspirin (3 g/d), and ibuprofen (1,200 mg/d) did not control the recurrent episodes of fever, urticaria, and bone pain. A clinical response was observed only with prednisone (50 mg/die) or cyclosporin (1 mg/Kg/ day).

The patient was followed for 8 years and in February 2001 he was still dependent on prednisone (50 mg/day) to control the disease relapses. The biclonal IgM-gammopathy remained stable, rheumatoid factor was negative, and the other laboratory studies were unchanged.

In April 2001 he was admitted to the hospital with a *Staphylococcus aureus* pneumonia, esophageal candidosis, hypertension, and a transient ischemic attack in the territory of the left middle-cerebral artery. At this time, the international normalized ratio was 1.4 (normal reference <1.2) and activated partial thromboplastin time was 61 sec. (normal reference 28-42). IgM anticardiolipin antibodies were recognized (12.3 U/mL, normal reference <6 U/ml) but screening for lupus anticoagulant was negative and blood levels of anti-β2-glycoprotein I IgG and IgM antibodies were 0.1 U/ml and 1.2 U/ml, respectively (normal reference <5 U/ml). We carried out a thrombophilia screen. Protein C, protein S, antithrombin III, and factor V Leiden were within normal limits and a search for the prothrombin G→A 20210 mutation and the methylenetetrahydrofolate reductase (MTHFR) C→T 667 variant was negative. Blood levels of homocysteine were 31.5 mmol/L (normal reference value < 15 mmol/L) with normal concentrations of vitamin B12 and folate. A transthoracic cardiac ultrasonography did not reveal intracardiac thrombus, septal defect, or valvular vegetation. The patient was treated appropriately and discharged on prednisone, losartan, atenolol, folate, vitamin B supplements, and aspirin in May 2001.

In July 2001 the patient was re-admitted with a pericardial effusion and retinal vasculitis with severe visual impairment; laboratory values were unchanged. The patient had a full recovery and was discharged free of symptoms in August 2001.

The patient's subsequent course was unremarkable until January 2002 when he suffered an ischemic stroke in the region of the left middle-cerebral artery and an acute non-Q wave myocardial infarction that was complicated by severe cardiogenic pulmonary edema and the adult distress respiratory syndrome. At this time, a search for anticardiolipin IgM antibodies was again positive (15.8 U/mL) and elevated blood levels of anti-β2-glycoprotein I IgM antibodies (61.6 U/ml) were also found. Anti-β2-glycoprotein I IgG antibodies were negative and the biclonal IgM gammopathy and IgM levels remained stable. Screening for other inherited or acquired thrombophilic factors disclosed only elevated blood concentrations of homocysteine (25.7 mmol/L).

The patient was admitted to the intensive care unit (ICU) and mechanically ventilated. Treatment included nitroglycerin, dopamine, enoxaparin, metoprolol, furosemide, proton-pump inhibitors, methylprednisolone, antibiotics, and total parenteral nutrition. A switch to warfarin was not possible as the patient was unable to ingest. After a prolonged stay in the ICU, he died in May 2002 with multiple organ failure; a necropsy was not done.

**Discussion**

Schnitzler's syndrome has a chronic course and most patients experience a favorable outcome (1). Less than 15% of them progress to a lymphoplasmacytic malignancy, such as Waldenström macroglobulinemia, lymphoplasmacytoid lymphoma or IgM myeloma (1). Instead complications arising from the chronic use of steroids, such as hypertension, diabetes and immune suppression, may have a greater impact on the patient's survival and the quality of life (1). The diagnosis is based upon the unique constellation of chronic urticaria, intermittent fever, bone pain, and arthralgia or arthritis combined with the presence of a monoclonal IgM gammopathy.

Skin biopsy in this case showed features consistent with neutrophilic urticaria, which is a typical finding in patients with Schnitzler's syndrome (1). However, when complement levels are lowered as observed in this patient, other conditions such as hypocomplementic urticarial vasculitis should be considered in the differential diagnosis. Complement deficiency is indeed uncommon among patients with Schnitzler's syndrome, even though low C4 levels have been observed in at least two previously reported cases (3). Systemic lupus erythematosus, adult onset Still's disease, chronic B hepatitis, cryoglobulinemia, hyper-IgD syndrome, acquired C1 inhibitor deficiency, and delayed pressure urticaria were easily ruled out in this case based on clinical presentation and laboratory studies.

The patient reported here exhibited the typical chronic course of the syndrome over a 10-year follow-up with a stable biclonal IgM gammopathy and no evidence of progression towards a lymphoproliferative disorder. However, there was no improvement with antihistamines, aspirin, ibuprofen, dapsone or colchicine and a clinical response was achieved only when the patient was given prednisone and cyclosporin. A recent study has indeed suggested that the use of cyclosporin could be a valuable therapeutic alternative, particularly in those patients in whom the histological examination of the urticarial lesions also shows features of leucocytoclastic vasculitis (4). Even interferon-α seems to be a promising strategy for the treatment of Schnitzler's syndrome (5), but we did not use it in this case. Our patient remained dependent on high-dose prednisone to control relapses over the long-term course of his disease and the chronic use of steroids was complicated by hypertension and the occurrence of severe infections. Moreover, after a long follow-up with stable disease, he entered an accelerated phase of clinical deterioration with repeated thromboses of the cerebral and coronary arteries that ultimately led to a fatal outcome. Venous or arterial thrombosis is an atypical clinical feature in patients with Schnitzler's syndrome, and indeed Lipsker and colleagues did not report any venous or arterial thrombotic events in their recent review of the published cases of the syndrome (1).

Many different factors could have contributed to the severe clotting disorder in the patient we describe. When the patient was admitted with a transient ischemic attack and bacterial pneumonia, anti-cardiolipin IgM antibodies were detected but we concluded that

the episode of cerebral thrombosis was caused by hyperhomocysteinemia and atherosclerosis due to hypertension and long-term treatment with high doses of prednisone rather than by an underlying antiphospholipid syndrome. We regarded the moderate titer of serum anti-cardiolipin as a false positive finding attributable to non-specific binding in the assay linked to the elevated blood levels of biclonal IgM. We decided against anticoagulation on this occasion and the patient was given aspirin.

Eight months later, he experienced a catastrophic thrombotic disorder with a stroke and an acute myocardial infarction and again anti-cardiolipin and anti-β2-glycoprotein I IgM antibodies at moderate to high levels were found. Even though we could not rule out the possibility that the positive titer of anti-cardiolipin IgM was due to interference by biclonal IgM, the fact remains that the Sapporo criteria for a diagnosis of definite antiphospholipid syndrome were fulfilled during the active clotting phase of the disease with two clinical episodes of arterial thrombosis and anti-cardiolipin IgM antibodies present on more than two occasions at least 6 weeks apart (6). At this stage, we decided to start anticoagulant treatment with enoxaparin but the subsequent course was complicated by multiple organ failure and ultimately the patient died.

It is unclear why this patient developed an anti-phospholipid syndrome during the course of an otherwise stable Schnitzler's syndrome. Anti-cardiolipin antibodies were first recognized during the admission for a bacterial pneumonia, making it conceivable that the respiratory infection with *S. aureus* was an important mechanism responsible for the production of anti-cardiolipin antibodies. Available data suggest that the production of anti-phospholipid antibodies may be a secondary phenomenon in the setting of infections; however in most of these cases such antibodies are transient and not generally associated with thrombosis (7, 8). To the best of our knowledge, there has been no previous report of the association of Schnitzler's syndrome with the antiphospholipid syndrome in the English literature.

Screening for other acquired thrombophilic factors repeatedly disclosed that the patient had elevated blood levels of homocysteine despite normal levels of both vitamin B12 and folate. Subjects with raised blood homocysteinemia have a significantly increased risk of cardiovascular and cerebrovascular disease compared to the general population (9). Homocysteine levels tend to decrease when patients are supplemented with folic acid and group B vitamins, but they remained elevated in this subject despite appropriate treatment. Anti-cardiolipin antibodies, hypertension or raised homocysteine could each explain the thrombotic events in this patient, but we believe that the extremely severe hypercoagulable state that led to the recurrent episodes of arterial thromboembolism was the result of their prothrombotic activity in combination rather than of each of them in isolation.

Our case report provides a first piece of evidence for the hypothesis that the association with immune-mediated or metabolic disorders, such as the antiphospholipid syndrome and hyperhomocysteinemia, may unfavorably affect the otherwise chronic and stable course of patients with Schnitzler's syndrome. The systemic clotting disorder, the association with the antiphospholipid syndrome and hyperhomocysteinemia, and the biclonal rather than monoclonal IgM gammopathy were striking features of this atypical case of Schnitzler's syndrome. We suggest that all patients should be routinely screened for antiphospholipid antibodies and hyperhomocysteine when the diagnosis of Schnitzler's syndrome is definitely established.

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